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Chinese Drugs of Plant Origin

Chemistry, Pharmacology,
and Use in Traditional and Modern Medicine

With 41 Figures

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Acanthopanax senticosus (Rupr. et Maxim.) Harms

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1.1 Introduction

Ciwujia, Radix *Acanthopanax senticosi*, is the dry root and rootstock of *Acanthopanax* (*Eleutherococcus*) *senticosus* (Rupr. et Maxim.) Harms (Araliaceae), which is collected in spring and fall. It is listed officially in the Chinese Pharmacopoeia and commonly known as "Siberian ginseng". It belongs to the same plant family as *Panax ginseng*. In addition, two galenic preparations of *A. senticosus* are also included in the Chinese Pharmacopoeia:

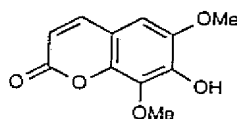
- Ciwujia Jingao, Extractum *Acanthopanax senticosi*, prepared by extraction of the powdered root of *A. senticosus* with 75% ethanol and concentration of the extract
- Ciwujia Pian, Tabellae *Acanthopanax senticosi*, prepared from the extract

The roots and rootstock of *A. senticosus* and its preparations have been used as a tonic in Chinese traditional medicine for a long time.

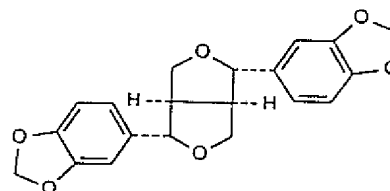
1.2 Chemical Constituents

From the roots and stems of *A. senticosus* collected in China, isofraxidin (1-1), sesamin (1-2), β -sitosterol (1-3), friedelin (1-4), and several polysaccharides have been isolated in addition to eleutherosides A, B (1-8), B₁ (1-9), C, D, E, I, K, L, and M [1]. The eleutherosides I, K, L, and M have also been isolated from the leaves of *A. senticosus* [2].

Isofraxidin is a derivative of coumarin, the lactone of coumarinic acid; sesamin is a lignan derivative; and β -sitosterol, a widely distributed plant sterol, has a stigmasterane (1-5) carbon skeleton, whereas friedelin belongs to triterpenes derived from D:A-friedooleanane (1-6).

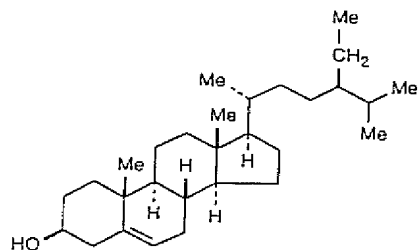


Isofraxidin (1-1)

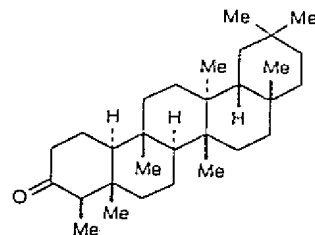


Sesamin (1-2)

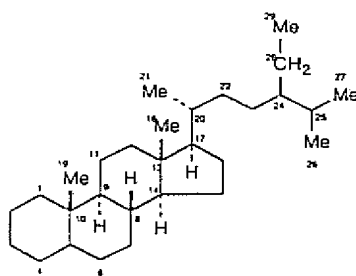
2 *Acanthopanax senticosus* (Rupr. et Maxim.) Harms



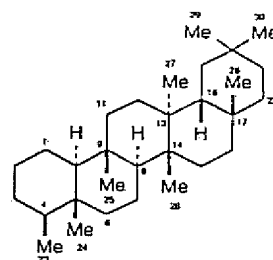
β -Sitosterol (1-3)



Friedelin (1-4)

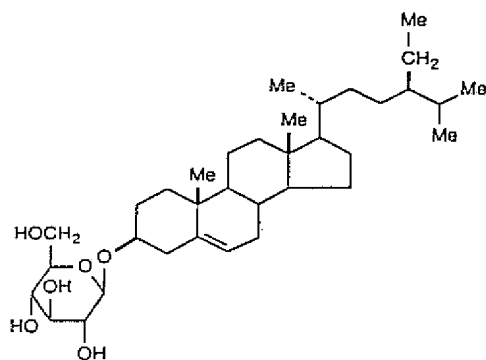


Stigmastane (1-5)

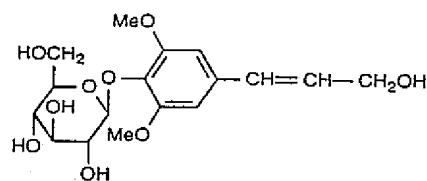


D:A-Friedooleanane (1-6)

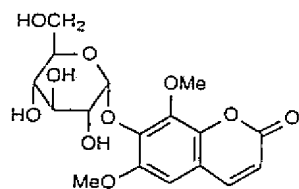
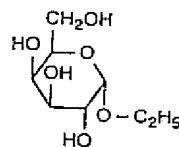
The eleutherosides are glycosides with different aglycones. Thus, eleutheroside A (1-7) is a steroid glycoside with β -sitosterol as the aglycone; eutherosides I (1-13), K (1-14), L (1-15), and M (1-16) are triterpene glycosides with oleanolic acid as the aglycone; and eleutherosides D (1-11) and E (1-12) are epimeric syringaresinol diglycosides. The other eleutherosides are glycosides with simple aglycones. The most simple eleutheroside is eleutheroside C (1-10), which is ethyl α -D-galactopyranoside. Eleutheroside B is identical to syringin.



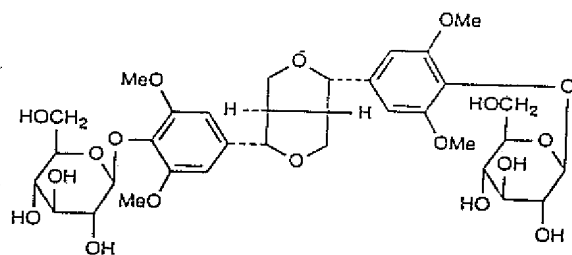
Eleutheroside A (1-7)



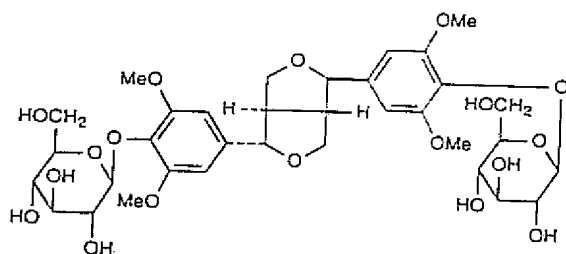
Eleutheroside B (1-8)

Eleutheroside B₁ (1-9)

Eleutheroside C (1-10)



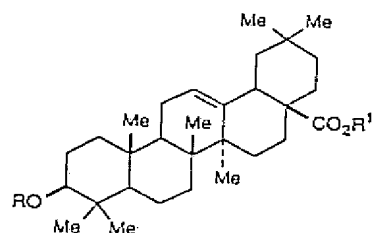
Eleutheroside D (1-11)



Eleutheroside E (1-12)

Recently, the isolation and structure determination of a series of minor saponins named ciwujianosides A₁, A₂, A₃, A₄, B, C₁, C₂, C₃, C₄, D₁, D₂, D₃, and E from the leaves of *A. senticosus* have been further reported. Like the eleutherosides, ciwujianosides A₁ (1-17), C₃ (1-18), C₄ (1-19) and D₁ (1-20) have oleanolic acid as aglycone. Ciwujianosides A₂ (1-21), B (1-22), C₁ (1-23), C₂ (1-24), D₂ (1-25), and E (1-26) have been found to possess 30-norolean-12,20(29)-dien-28-oic acid as aglycone, whereas the aglycone for ciwujianosides A₃ (1-27), A₄ (1-28), and D₃ (1-29) has been found to be mesembryanthemoidigenic acid [28, 29].

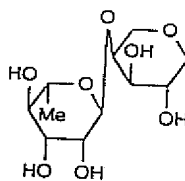
4 *Acanthopanax senticosus* (Rupr. et Maxim.) Harms



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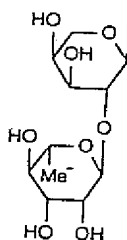
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Eleutheroside I (1-13)



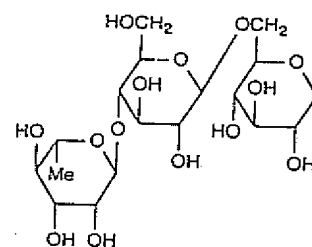
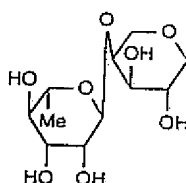
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Eleutheroside K (1-14)

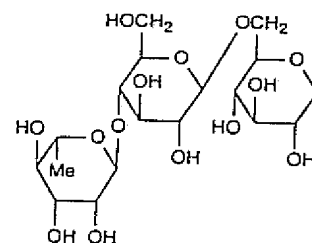
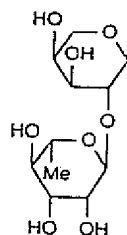


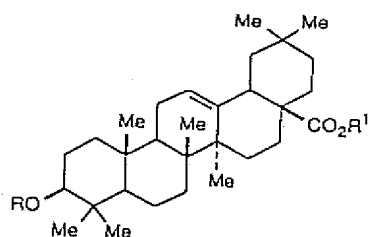
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Eleutheroside L (1-15)



Eleutheroside M (1-16)

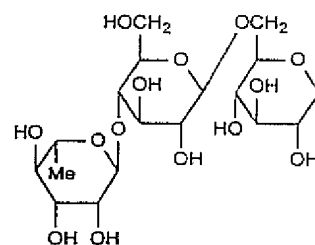
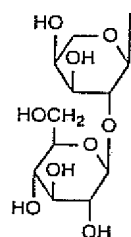




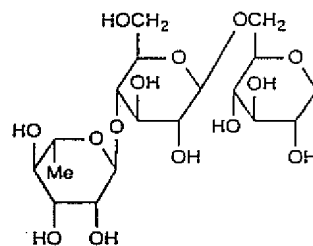
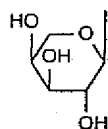
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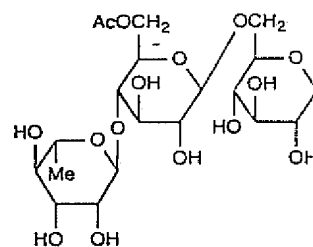
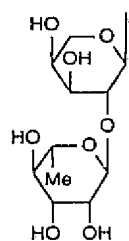
Ciwujianoside A₁ (1-17)



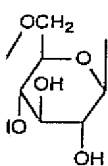
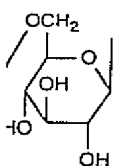
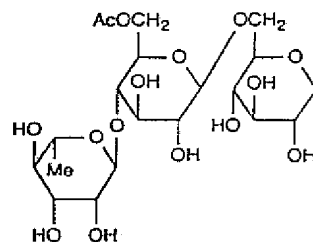
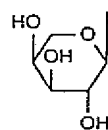
Ciwujianoside C₃ (1-18)

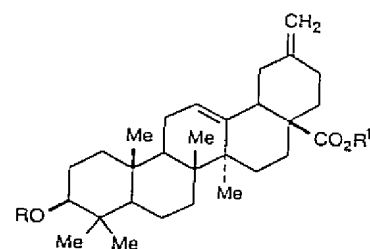


Ciwujianoside C₄ (1-19)



Ciwujianoside D₁ (1-20)

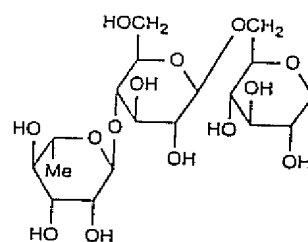
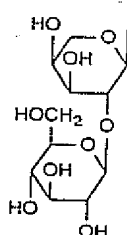




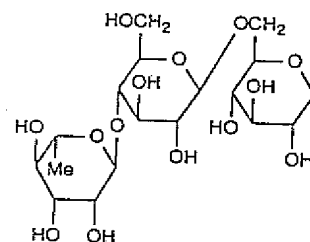
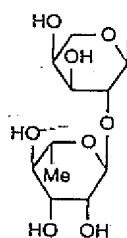
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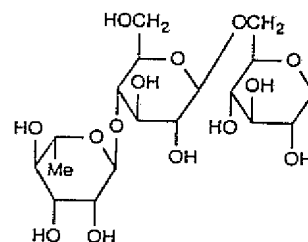
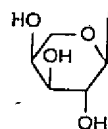
Ciwujianoside A₂ (I-21)



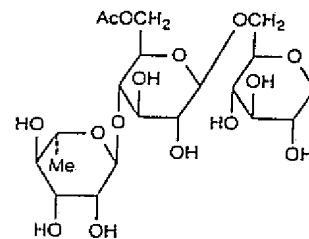
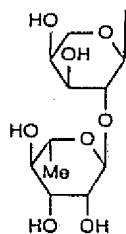
Ciwujianoside B (I-22)

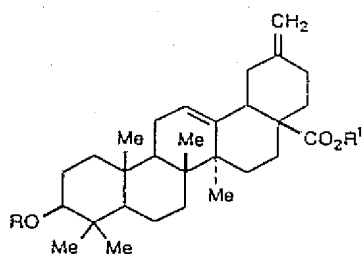


Ciwujianoside C₁ (I-23)



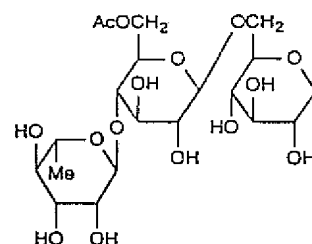
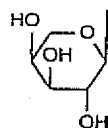
Ciwujianoside C₂ (I-24)





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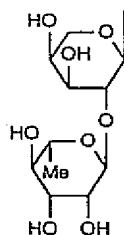
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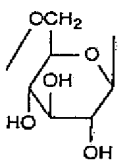
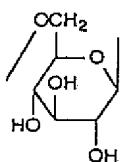
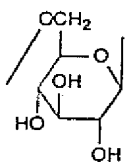
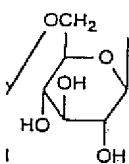
Ciwujianoside D₂ (1-25)

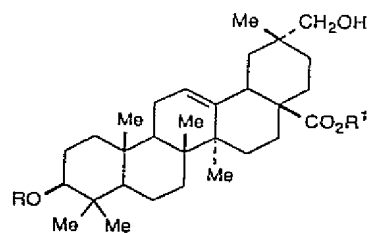
Ciwujianoside E (1-26)

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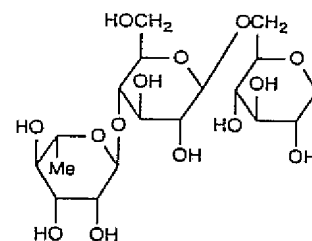
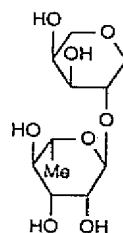




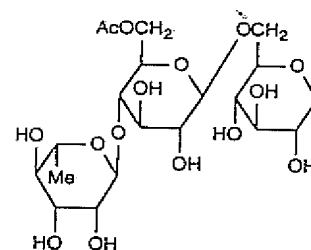
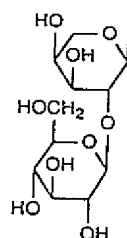
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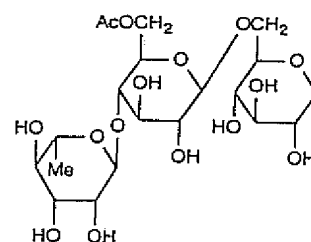
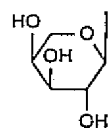
Ciwujianoside A₃ (1-27)



Ciwujianoside A₄ (1-28)



Ciwujianoside D₃ (1-29)



Furthermore, the isolation of 3,4-dihydroxybenzoic acid [3] and a number of glycans referred to as eleutherans A, B, C, D, E, F, and G [4] have also been reported.

The amount of syringin, isofraxidin, and total flavones were highest in the root, rhizome, and stem. Syringin and isofraxidin were not found in the leaf and fruit, whereas a large amount of total flavone was present in the leaf. The amounts of the above mentioned constituents in the root, rhizome, and stem were highest during May and October and lowest in July. The amounts were also different in *A. senticosus* collected from various geological regions [5]. In the root and rhizome of *A. senticosus* a syringin yield of 0.03% was obtained [6]. The syringin content in powdered roots or rhizomes decreased to 50% of the original value after 12 months storage and could no longer be detected after 3 years of storage under regular conditions [7].

1.3 Pharmacology

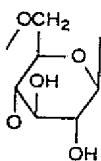
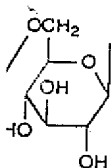
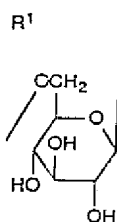
The water extract of *A. senticosus* prevented stress-induced decreases in rectal temperature and body and grip tonus and accelerated recovery from decreases in body and grip tonus in acutely stressed mice. These effects were attributed to syringin and syringaresinol-di-*O*-glucoside [8]. The water extract and syringaresinol also protected mice from stress-induced decreases in sex behaviour. They had no effect, however, on stress-induced increases in tyrosine hydroxylase activity in adrenal gland and hypothalamic regions and on corticosterone contents in adrenal gland and serum [9].

The extract of *A. senticosus* at a single i. p. dose of 40–320 mg/kg or at a dosage of 80–320 mg/kg within 4–5 days produced a sedative effect, resulting in increased sleep duration. It was also shown to produce an inhibition of hexobarbital metabolism in vitro, supporting enzyme inhibition rather than enzyme induction as a mechanism for its actions [10].

The alcohol extract of *A. senticosus* inhibited protein synthesis in cell-free rat liver microsomal systems to a greater extent than in polyribosomal systems. This effect was found to be concentration dependent. The water extract had less inhibitory activity and the pure glycosides, eleutherosides B and D, inhibited protein synthesis 10–20 times more than did the alcohol extract [11]; however, i.p. administration of the alcohol extract to rats stimulated protein biosynthesis in the pancreas, liver, and adrenal glands. The results are consistent with the observation that high levels of eleutheroside accumulate in adrenal glands [12].

Intraperitoneal administration of an extract containing mainly eleutherosides B and D to mice at daily dose of 18 mg/animal for 1 week increased the cytostatic activity of natural killer cells by about 200%. It appeared that the eleutherosides stimulated macrophagal T cell and possibly B cell mediated immunity [13]. A recent study on the immunomodulatory activity of the ethanol extract of *A. senticosus* administered orally to healthy volunteers for 4 weeks, showed a drastic increase in the absolute number of immune competent cells, especially T lymphocytes. No side effects were observed within 6 months [14].

Treatment of rats with an extract of *A. senticosus* for 14 days before γ -irradiation accelerated the restoration of blood nucleic acid levels to normal, delayed the nadir in blood leukocyte count for 1–3 days, and increased leukocyte count on days 10–30



after radiation compared to untreated, irradiated controls. The extract thus appeared to promote recovery from radiation effects rather than to protect against them [15]. Use of an aqueous extract of *A. senticosus* in combination with either cytarabine or N^6 -(Δ^2 -isopentenyl)adenosine had additive antiproliferative effects on L 1210 leukemia cells in vitro [16].

A crude polysaccharide component, PES, was obtained in 0.5% yield by treatment of a hot ethanol extract of powdered roots of *A. senticosus* with acetone. Polysaccharide components PES-A and PES-B were separated by chromatography of crude PES on DEAE-Sephadex A-25 and elution with water and 0.1 and 0.25 N NaCl solutions. PES-A and PES-B were recovered in 0.1 N and 0.25 N NaCl fractions, respectively, and further purified on DEAE-cellulose DE-32 to a final yield of 0.01% and 0.001% of the root, respectively. Gel filtration on Sephadex G-150 and G-200 showed molecular weights of 7000 for PES-A and of 76 000 for PES-B. Both PES-A and PES-B contained glucose, galactose, and arabinose. The molar ratios of glucose:galactose:arabinose were 33:2:1 for PES-A and 2:9:18 for PES-B [17]. The crude polysaccharide PES and the separated and purified components PES-A and PES-B were effective immunostimulating agents. They potentiated the antibody response against sheep red blood cells and stimulated phagocytosis by peritoneal macrophages of mice. They were also found to decrease toxic effects of thioacetamide and phytohemagglutinin in mice and to enhance resistance to X-ray irradiation [18]. Intraperitoneal administration into mice of PES at a dosage of 125 mg/kg for 5 days simultaneously with 0.2 mg bovine serum albumin (BSA) per animal markedly increased the serum levels of anti-BSA IgG and total anti-BSA antibodies but not the serum level of total IgG indicating that PES stimulates the immune activity of mice against invading foreign substances [19]. In vitro the polysaccharides caused a five- to tenfold increase in interferon titer in S 801 and S 7811 leukemic cell cultures [20].

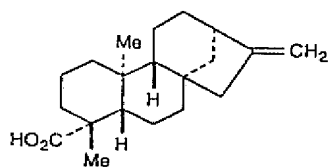
In addition, a homogeneous glucan with a mean molecular weight of 150 000 and homogeneous heteroxylan with a mean molecular weight of 30 000 were isolated from an alkaline aqueous extract of *A. senticosus* by DEAE-Sepharose CL-6B and Sephacryl S-400 column chromatography. The crude polysaccharide mixture and the heteroxylan stimulated phagocytosis in in vitro and in vivo tests [21].

Furthermore, the glycans eleutheran A-G exerted a marked hypoglycemic effect in normal and in alloxan-induced hyperglycemic mice [4]. 3,4-Dihydroxybenzoic acid and its ethylester inhibited rat platelet aggregation [3].

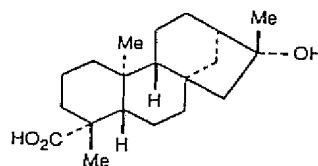
1.4 *Acanthopanax gracilistylus*

Wujiapi. Cortex *Acanthopanax*, is another item derived from the *Acanthopanax* plant and listed officially in the Chinese Pharmacopoeia. It is the dry root bark of *A. gracilistylus* W. W. Smith. The roots are collected in summer and fall, and the rootbark is peeled off and dried. It is used as an antirheumatic, antiedemic, and tonic preparation.

From the root bark of *A. gracilistylus*, sesamin, β -sitosterol, syringin, β -sitosterolglucoside, eleutheroside B₁, kaurenoic acid (1-30) 16- α -hydroxy-kauran-18-oic acid (1-31), and stearic acid have been isolated and identified [22, 23].



Kaurenoic acid (1-30)

16- α -Hydroxy-kauran-18-oic acid (1-31)

The total glycoside fraction isolated from *A. gracilistylus* var. *pubescens* was administered i.v. to rabbits with acute myocardial ischemia produced by coronary artery occlusion. A significant decrease in heart rate and blood pressure was seen. The lactic acid concentration and creatine kinase activity were also significantly decreased. The total ST segment elevation within 8 h, the number of total pathologic Q waves, and the infarct size determined by precordial electrocardiogram mapping were markedly reduced [24].

The pharmacokinetics of eleutheroside B, one of the major active principles of *A. senticosus* has been studied. Tritiated eleutheroside B (5 mg/kg) was administered to rats i.p. Maximal levels of radioactivity were observed in blood 15 min after treatment. Urinary excretion of radioactivity reached 35%, 55%, and 90% of the administered dose at 2, 4, and 48 h, respectively. Only 2.5%–3.0% of the administered dose was excreted in the feces [25, 26]. Eleutheroside B is strongly bound to blood serum globulins and albumins and to a much lesser extent to lipids [27].

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¹ Some of the works cited in this and in many subsequent reference lists are also summarized in *Chemical Abstracts*. In each case the appropriate citation is given in parentheses at the end of the reference.

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